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EDITORIAL COMMENT

Evolution of Stroke Prevention in Nonvalvular Atrial Fibrillation Patients*

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The PREVAIL (Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) trial is the latest in the series of studies evaluating left atrial appendage (LAA) occlusion with the Watchman device (Boston Scientific, Natick, Massachusetts) as an alternative to warfarin therapy for the prevention of stroke in patients with nonvalvular atrial fibrillation (NVAF). The PREVAIL trial was initially designed as a follow-up study to PROTECT AF (Watchman Left Atrial Appendage Closure Technology for Embolic Protection in Patients With Atrial Fibrillation), which demonstrated noninferiority to warfarin in preventing stroke (1). However, the U.S. Food and Drug Administration (FDA) raised concerns regarding acute safety

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events and the selection of low stroke risk patients ($CHADS_2$ score of 1). In addition, many patients in PROTECT AF were treated with chronic clopidogrel and/or remained on warfarin >45 days after device implantation. Thus, at the request of the FDA, the PREVAIL study was designed to address the limitations of PROTECT AF and to assess the safety and efficacy of LAA occlusion for stroke prevention compared with long-term warfarin therapy in patients with NVAF.

Despite the limitations of PROTECT AF, the FDA recognized the value in the study's data. Therefore, the FDA and the sponsor developed a Bayesian trial design for the PREVAIL trial, taking into consideration data from PROTECT AF. In addition, data from PROTECT AF continued to be collected to provide long-term safety and effectiveness information on the LAA occlusion device.

As discussed by Holmes et al. (2) in this issue of the *Journal*, the primary endpoints for the PREVAIL trial included: 1) the primary efficacy composite of hemorrhagic or ischemic stroke, systemic embolism, and cardiovascular/unexplained death; 2) the late-ischemic efficacy composite of ischemic stroke or systemic embolism, excluding the first 7 days after randomization; and 3) the early safety composite of all-cause death, ischemic stroke, serious adverse event, or device-/procedure-related events requiring open cardiovascular surgery or major endovascular intervention. The PREVAIL trial did not achieve the pre-specified noninferiority criteria for its primary efficacy endpoint. Contributing to the failure of the PREVAIL trial to meet its primary efficacy endpoint was the duration of the trial and the low event rate in the control group. The PREVAIL trial did achieve its safety endpoint, and its secondary primary endpoint was met for rate difference but not for risk ratio.

The authors of PREVAIL should be commended, along with all the participating investigators, not only for their contribution to this article (2), but to the series of Watchman studies. Taken in totality, the Watchman studies are the first to demonstrate, in a prospective randomized fashion, the utility of exclusion of LAA in preventing stroke in patients with NVAF compared with warfarin. On the basis of the efficacy data from the initial PROTECT AF trial, the improved mortality data of the 5-year follow-up from PROTECT AF, the improved safety results of the Continued Access PROTECT AF Registry, and the safety data from PREVAIL, an FDA panel recently voted 13 to 1 to approve the Watchman device for use in patients with NVAF.

Although the Watchman studies provide the proof of principle that LAA exclusion is effective in

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preventing stroke in patients with NVAF, LAA device implants should not be considered universally as a substitute for oral anticoagulation therapy. The newer oral anticoagulation drugs demonstrate equivalent-to-superior benefit in preventing cardioembolic strokes while having less bleeding risk compared with warfarin (3–6). In a recent meta-analysis of 4 new oral anticoagulants, all 71,683 participants included in the RE-LY (Randomized Evaluation of Long Term Anticoagulant Therapy), ROCKET AF (Rivaroxaban Once-daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation), and ENGAGE AF-TIMI 48 (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48) trials were compared for stroke and systemic embolic events, ischemic stroke, hemorrhagic stroke, all-cause mortality, myocardial infarction, major bleeding, intracranial hemorrhage, and gastrointestinal bleeding (7). A comparison of new high-dose oral anticoagulants versus warfarin demonstrated: 1) significantly reduced composite stroke or systemic embolic events (by 19%), the benefit of which was mainly driven by a large reduction in hemorrhagic stroke; 2) a 14% nonsignificant reduction in major bleeding, a reflection of decreased intracranial hemorrhage; 3) a significant reduction in all-cause mortality; and 4) acknowledgment that the drugs were similar to warfarin in the prevention of ischemic stroke and myocardial infarction.

An analysis of lower doses of dabigatran and edoxaban compared with warfarin demonstrated: 1) an increase in ischemic stroke versus warfarin, which was balanced by a large decrease in hemorrhagic stroke; 2) a significant reduction in all-cause mortality; 3) significantly more myocardial infarctions; 4) a nonsignificant reduction in major bleeding but with a significant reduction in intracranial hemorrhage; and 5) similar gastrointestinal bleeding (7).

The introduction of LAA exclusion devices and the newer oral anticoagulants offers improved therapies for preventing stroke in patients with NVAF. However, the treatment of the most vulnerable patients who have an increased risk of both ischemic and bleeding events, namely the elderly patient (aged ≥75 years), patients with a history of stroke, and those with renal dysfunction, must thoroughly evaluate the benefits and risks of device implantation versus oral anticoagulation therapy. The initial embolic risks and adverse events associated with the Watchman device implantation cannot outweigh the long-term bleeding risks of the newer oral anticoagulation drugs. In highly skilled centers in which LAA exclusion is routinely performed, the procedural risks in elderly patients do not seem to differ from younger patients (8). Until additional data become available for these high-risk patients, the decision to treat them with an LAA occlusion device instead of oral anticoagulation therapy should be made on the basis of the patient's overall health, ability to tolerate oral anticoagulation therapy, procedural risks, and the operator's experience.

One group of patients who have not been sufficiently evaluated are those with contraindications to oral anticoagulants. The majority of these patients were excluded from both the Watchman studies and the newer anticoagulant trials. Despite lower bleeding rates with the newer anticoagulant agents, significant bleeding still occurs in 2% to 3% of treated patients (3–6). Patients with a contraindication to oral anticoagulation therapy are presently not considered candidates for the Watchman device. Although the results of the ASAP (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology) study suggest that the Watchman device can be safely implanted after treatment with aspirin and clopidogrel rather than a warfarin transition, the study was small and observational in nature (9). Percutaneous epicardial LAA exclusion with the LARIAT device (SentreHEART, Inc., Redwood City, California) or minimally invasive surgery with the AtriClip device (AtriCure, Inc., West Chester, Ohio) have been used for LAA exclusion for patients with contraindications to oral anticoagulants (10,11). However, prospective, randomized studies are required to fully assess the utility of LAA exclusion without the use of short-term oral anticoagulation therapy in this group of patients.

Complications, such as the observed 4% thrombus formation on the Watchman device (1,9), progression of leak size (12), and case reports of late thrombus formation (13), suggest the need for long-term surveillance with transesophageal echocardiography (TEE). A 45-day post-procedure TEE should be performed to assess for leaks and thrombus before discontinuing warfarin. Longer term surveillance TEEs at 1-year intervals should be considered if there is a leak or a partial uncovered LAA lobe, as there have been reports of late thrombus formation after 3 years, in addition to lack of endothelialization of an implanted Watchman device and the potential of device erosion through the LAA (13,14). These observations and the fact that cardioembolic events can arise from non-LAA origins highlight consideration of a hybrid approach of LAA occlusion and lower doses

of the newer anticoagulants for the treatment of stroke in AF patients.

PREVAIL attempted to address the learning curve by including new operators who performed the device implantation in nearly 40% of the randomized patients. The safety results between experienced and new operators were similar, suggesting that the sponsor's training program was adequate. However, the number of new sites was small, and cases were performed in a controlled environment. Commercialization of the Watchman device will require similar judicious training of new operators and a controlled rollout of the product. Proper training is necessary to increase the safety of device implantation and increase the likelihood of proper Watchman deployment. An argument can be made that with the introduction of any new technology, dissemination of the therapy should be localized at "centers of excellence." Identifying operators with the necessary skillset to implant the Watchman device will be paramount for the long-term success of LAA exclusion as a treatment for stroke in AF patients.

Despite the concerns and unanswered long-term sequelae of device implantation, with proper patient selection, the conclusion by Holmes et al. (2) should be considered: LAA occlusion is a reasonable alternative to warfarin for stroke prevention in patients with NVAF who do not have an absolute contraindication to short-term warfarin demonstrates the evolution of stroke prevention in patients with AF.

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